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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,085	05/03/2006	Shinji Okano	50026/058001	5137

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/578,085	OKANO ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,5-7,10,11,13-21,23-25 and 30-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,5-7,10,11,13-21,23-25 and 30-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :7/15/2010;4/14/2010;12/30/09;12/10/09.

DETAILED ACTION

Applicant's amendment filed on 4/28/2010 was entered.

Amended claims 2, 5-7, 10-11, 13-21, 23-25 and new claims 30-34 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The rejection under 35 U.S.C. 112, first paragraph, was withdrawn in light of Applicant's amendment.

The rejection under 35 U.S.C. 102(b) as being anticipated by Jin et al. (Gene therapy 10:272-277, February 2003; IDS) as evidenced by Romani et al. (J. Exp. Med. 180:83-93, 1994; Cited previously) was withdrawn in light of Applicant's amendment with the new limitation "An isolated CD11c+ precursor of an immature dendritic cell".

Information Disclosure Statement

All of the documents listed in the information disclosure statements (IDS) submitted on 4/14/2010 and 7/15/2010 have been considered by the examiner. However, the English translation documents were crossed out because they are not proper references to be printed on the first page of an issued US patent.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Amended claims 2, 10-11, 19, 23-25 and new claims 30-31, 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Gary-Gouy et al (J. Interferon and Cytokine Res. 22:653-659, 2002; IDS). ***This is a modified rejection necessitated by Applicant's amendment particularly with the recited limitations "CD11c+ immature dendiric cell"; "CD11c+ mature dendritic cell" and "CD11c+ precursor cell of a dendritic cell".***

Gary-Gouy et al already described at least the isolation of plasmacytoid dendritic cells (CD123+CD11c-) and CD11c+ myeloid dendritic cells from healthy human blood donors who are negative for HTLV-1, HIV, hepatitis B and C viruses, and incubated each of the isolated cell population in the absence or presence of cytokines prior to infection with Sendai virus which is a vector (see at least the sections titled "Cell purification" and "Type 1 IFN assay" on page 654 and the section titled "Monocytes and CD123hi PDC but not CD11c+ MDC produce IFN-1 on specific stimulation" on page 655). The plasmacytoid cells are known to be predendritic cells (PDC) or DC precursor cells (page 653, col. 1 continues to first paragraph of col. 2). Since there is no indication or suggestion that isolated CD11c+ myeloid dendritic cells of Gary-Gouy express markers such as CD80, CD83 and CD86 nor were the isolated CD11c+

myeloid dendritic cells subjected to stimulation or activation by agents such as LPS and that they were fractionated or sorted from the same cell population containing CD123+CD11c- DC precursor cells; they fall within the scope of "immature dendritic cells" as defined by the present application (see at least page 10, lines 16-20; page 11, lines 14-19). Moreover, CD11c+ marker is a cell surface marker of immature dendritic cells and since CD11c+ myeloid dendritic cells of Gary-Gouy were fractionated and sorted using anti-CD11c-FITC; the isolated/fractionated cell population must contain at least immature dendritic cells. The CD11c+ myeloid dendritic cells were infected with Sendai virus; and 18 h later IFN-1 production was assayed (see the section titled "Monocytes and CD123hi PDC but not CD11c+ MDC produce IFN-1 on specific stimulation" on page 655; and Table 1).

Accordingly, the isolated CD11c+ myeloid dendritic cell populations infected with Sendai virus at different time points during the 18 h incubation periods (e.g., 5 min, 15 min, 30 min, 1 hr, 2 hrs, 10 hrs…) for IFN-1 production assay contain CD11c+ immature dendrictic cells comprising a Sendai virus vector and CD11c+ mature dendritic cells comprising a Sendai virus vector; that are indistinguishable from the isolated CD11c+ dendritic cells (immature and/or mature) comprising a Sendai virus vector as broadly claimed. Additionally, it should be noted that the spontaneous maturation of immature dendritic cells to matured dendritic cells and/or introduction efficiency of 70% or more in immature dendritic cell is the inherent property of a Sendai virus vector; and therefore the method taught by Gary-Goury is also indistinguishable from the method as broadly claimed because it contains the same method step and the same starting materials.

Furthermore, please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, **or** are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Therefore, the reference anticipates the instant claims.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 4/28/2010 (page 9) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue that the reference fails to give no information about the maturation stage of the dendritic cells used in the experiment, including the absence of information about the expression of the CD80, CD83 and CD86 marker; and therefore the reference doe not describe immature dendritic cells as recited in the claims.

Once again, since at least isolated CD11c+ myeloid dendritic cells of Gary-Gouy were not subjected to stimulation or activation by any agents such as LPS and that they

were fractionated or sorted from the same cell population containing CD123+CD11c- DC precursor cells; they should contain immature dendritic cells. Moreover, there is no indication or suggestion that the isolated CD11c+ myeloid dendritic cells of Gary-Gouy express CD80, CD83 and CD86 surface markers which are markers of mature dendritic cells. Furthermore, CD11c+ marker is a cell surface marker of immature dendritic cells and since CD11c+ myeloid dendritic cells of Gary-Gouy were fractionated and sorted using anti-CD11c-FITC; the isolated/fractionated cell population **must contain at least immature dendritic cells**. This is also supported by **the complete lack of IFN-I detection in CD11c+ myeloid dendritic cells prior to infection by Sendai virus (see Table 1)** since Lopez et al (JID 187:1126-1136, April 1 2003; IDS) already taught **that there is a strong correlation exists between murine DC maturation and the induction of IFN, although secreted IFN is not necessary for DC maturation**. The simple lack of disclosed information about the expression of CD80, CD83 and CD86 markers does not mean that isolated CD11c+ myeloid dendritic cells of Gary-Gouy must have all been activated and mature and express these specific cellular markers.

Accordingly, the isolated CD11c+ myeloid dendritic cell populations infected with Sendai virus at different time points during the 18 h incubation periods (e.g., 5 min, 15 min, 30 min, 1 hr, 2 hrs, 10 hrs…) for IFN-1 production assay contain CD11c+ immature dendrictic cells comprising a Sendai virus vector and CD11c+ mature dendritic cells comprising a Sendai virus vector; that are indistinguishable from the isolated CD11c+ dendritic cells (immature and/or mature) comprising a Sendai virus vector as broadly claimed. Additionally, it should be noted that the spontaneous maturation of immature

dendritic cells to matured dendritic cells and/or introduction efficiency of 70% or more in immature dendritic cell is the inherent property of a Sendai virus vector; and therefore the method taught by Gary-Goury is also indistinguishable from the method as broadly claimed because it contains the same method step and the same starting materials.

Amended claims 11, 16-19 and 24 are rejected under 35 U.S.C. 102(e) as being anticipated by Pickles et al (US 2005/0048030; IDS). ***This is a modified rejection necessitated by Applicant's amendment.***

The examiner interprets claims 11, 16-19 to be **product-by-process claims**.

Pickles et al teach at least a method for transferring a nucleotide sequence to a cell *in vitro* or *ex vivo* using a recombinant paramyxovirus vector, wherein the cell can be a human dendritic cell (see at least paragraphs 122-130), the recombinant paramyxovirus vector includes Sendai virus vector (at least paragraphs 43-45) and the nucleotide sequence encodes a cytokine such as beta-interferon or a tumor antigen (paragraphs 86, 92-103). It should be noted that the transfected dendritic cells that are taught by Pickles et al are inherently mature dendritic cells regardless whether the dendritic cells are mature and/or immature prior to transfection because of the spontaneous maturation of immature dendritic cells to matured dendritic cells by a Sendai virus vector. Additionally, since CD11c+ is an inherent cellular marker of a mature dendritic cell, the dendritic cells of Picles et al that were transfected with Sendai virus vector must also express CD11c+; and therefore they are indistinguishable from the isolated mature dendritic cell as claimed.

Once again, please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, **or** are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Therefore, the reference anticipates the instant claims.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 4/28/2010 (pages 9-11) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

Applicants argue basically that the reference fails to describe CD11c+ mature dendritic cells in the amended claims. Applicants further argue that the disclosure of Pickles is not an enabling disclosure of the subject matter because the susceptibility of a cell to the virus varies from virus to virus since some viruses infect the cell from the basolateral surface and others do not. Pickles failed to use Sendai virus or dendritic

cells in any of the examples. Therefore, the reference does not anticipate the instant claims.

Firstly, the transfected dendritic cells that are taught by Pickles et al are inherently mature dendritic cells regardless whether the dendritic cells are mature and/or immature prior to transfection because of the spontaneous maturation of immature dendritic cells to matured dendritic cells by a Sendai virus vector. Additionally, since CD11c+ is an inherent cellular marker of a mature dendritic cell, the dendritic cells of Picles et al that were transfected with Sendai virus vector must also express CD11c+; and therefore they are indistinguishable from the isolated mature dendritic cell as claimed.

Secondly, there is nothing that is unpredictable about transfecting dendritic cells with a recombinant Sendai virus, particularly dendritic cells in culture or in vitro as evidenced at least by the teachings of Gary-Gouy et al (J. Interferon and Cytokine Res. 22:653-659, 2002; IDS) which showed that Sendai virus infect isolated plasmacytoid dendritic precursor cells (CD123+CD11c-), CD11c+ myeloid dendritic cells and monocytes from human blood donors, wherein the cell populations were exposed to cytokines prior to or after infection with the Sendai virus. Additionally, Jin et al. (Gene therapy 10:272-277, February 2003; IDS) also demonstrated successfully that recombinant Sendai virus transfected highly efficiently in human cord-blood derived CD34+ cells which are precursor cells of dendritic cells. Furthermore, Lopez et al (JID 187:1126-1136, April 1 2003; IDS) already demonstrated clearly that **negative-strand RNA viruses infected successfully immature dendritic cells, including the use of**

Sendai viruses Cantell and 52. Importantly, Lopez demonstrated that while the Sendai Cantell virus is a very potent inducer of IFN in immature dendritic cells, the Sendai 52 is a very poor inducer of this pathway (see at least the section entitled "Type I IFN secretion by DCs infected with influenza or Sendai viruses" on page 1128 and Table 1). **Please note that about 75% and 85% of the isolated dendritic cells of Lopez do not express CD80 and CD86, respectively prior to infection with negative-strand RNA viruses (Table 4)**.

Thirdly, there is no requirement whatsoever that US patent application of Pickles et al has to provide working examples for something that is well known in the prior art, for this instance the ability of Sendai virus to infect dendritic cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 2, 5-7, 10-11, 13-21, 23-25 and 30-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Song et al. (US 2002/0123479 A1) in view of Tokusumi et al. (US 6,746,860; IDS), Jin et al. (Gene therapy 10:272-277, February 2003; IDS), Hwu et al (US 6,734,014) and Waller et al (US 2005/0013810). ***This is a slightly modified rejection necessitated by Applicant's amendment.***

Song et al disclose compositions and methods useful for stimulating an immune response against one or more disease associated antigens, including cancer associated antigens, by **genetically modifying dendritic cells including dendritic progenitor cells as well as dendritic cells having CD11c+ maker, *in vivo* or *ex vivo*, wherein the dendritic cells were genetically modified by a recombinant negative strand RNA virus (e.g., vesicular stomatitis virus, paramyxoviruses, orthomyxoviruse and bunyaviruses) directing the expression of at least one disease associated antigen** (see at least Summary of the Invention; particularly paragraphs 6-7, 9-12, 16-18, 41-45, 60 and Figure 1). Since the starting dendritic cells (including both dendritic cells and dendritic progenitors) used by Song et al do not express markers such as CD80, CD83 and CD86 (see at least Figure 1 for cellular dendritic cell markers taught by Song et al; paragraphs 9, 41-44), they fall within the scope of "immature dendritic cells" as defined by the present application (see at least page 10, lines 16-20; page 11, lines 14-19). It is further noted that the transfected dendritic cells were not further

subjected to any additionally treatment such as LPS stimulation for high expression of matured dendritic cell markers of CD80, CD83 and CD86. **Song et al also disclose that it has been discovered that the efficiency of immune system stimulation mediated by genetically modifying dendritic cells can be several orders of magnitude greater than that mediated by genetically modified fibroblasts, muscle, and other cell types** (paragraph 39). Song et al further disclose that an expression vector may in addition to directing expression of at least one disease associated antigen, directs the expression of an immunomodulatory factor such as IL-12, IL15, IL-2, beta-interferon among many others (paragraphs 68, 89-90). Song et al also teach that the genetically modifying dendritic cells, including allogeneic cells, are typically administered via parenteral or other traditional direct routes or directly into a specific tissue such as into the tumor in the case of cancer therapy in a mammal (e.g., a human) in need thereof (paragraphs 16-18, 43, 140, 164 and 176).

Song et al did not teach explicitly the use of a Sendai virus vector for genetically modifying immature dendritic cells, including dendritic progenitor cells, even though they disclosed that dendritic cells, including dendritic progenitor cells could be genetically modified by any recombinant negative strand RNA virus including any paramyxovirus; nor did Song et al teach specifically the use of CD34+ dendritic precursor cells and the step of further culturing the CD34+ precursor cells with GM-CSF and IL-4.

However, at the effective filing date of the present application, Tokusumi et al already disclosed the preparation of at least a recombinant Sendai virus vector to be used for transfer of foreign genes (see at least the abstract as well as Summary of the

Invention). Tokusumi et al further disclosed that **the Sendai virus vector is useful for gene therapy due to its safety, high gene transfer efficiency and capacity to express a foreign gene in a high level**.

Additionally, Jin et al already disclosed successfully a method in which recombinant Sendai virus was in contact and provided **a highly efficient gene transfer into human cord blood CD34+ cells**, including human cord blood HSCs and more immature cord blood progenitor cells (see at least the abstract; page 276, col. 1, last paragraph).

Moreover, Hwu et al also taught at least a method of preparing **recombinant dendritic cells by transforming a hematopoietic stem cell, including CD34+ cells derived from a variety of sources such as cord blood, bone marrow and mobilized peripheral blood, with a nucleic acid followed by differentiation of the stem cell into dendritic cells in the presence of GM-CSF, TNF-alpha and optionally together with IL-4** (see at least the abstract; col. 9, lines 29-57; col. 10, line 60 continues to line 13 of col. 11; col. 15, lines 15-46).

Furthermore, Waller et al also taught that progenitors of dendritic cells or immature dendritic cells can be identified in many tissues, such as bone marrow and blood, based on the expression of certain cell surface markers; and that dendritic cell progenitors are typically identified by the expression of one or more of the following markers on its cell surface **CD11c**, CD13, CD14, CD33, **CD34** or CD4 (see at least paragraphs 24-28 and 36).

Accordingly, it would have been obvious and within the scope of skill for an ordinary skilled artisan to modify the teachings of Song et al. by also utilizing a recombinant Sendai virus vector for genetically modifying immature dendritic cells, including CD11c+ and/or CD34+ dendritic precursor cells derived from bone marrow or cord blood to produce mature dendritic cells expressing at least a recombinant disease associated antigen as encompassed by the instant claims in light of the teachings of Tokusumi et al., Jin et al, Hwu et al and Waller et al as discussed above.

An ordinary skilled artisan would have been motivated to carry out the above modifications because Tokusumi et al already taught that the recombinant Sendai virus vector is useful for gene therapy due to its safety, high gene transfer efficiency and capacity to express a foreign gene in a high level. Additionally, a highly efficient gene transfer in human cord blood CD34+ cells which are dendritic precursor cells has been successfully achieved and demonstrated by Jin et al. Furthermore, dendritic cell progenitors typically identified at least by the expression of one or more of the following markers on its cell surface such as **CD11c** or **CD34**, derived from a variety of sources such as cord blood, bone marrow and mobilized peripheral blood, have been genetically modified for the preparation of mature dendritic cells expressing desired heterologous proteins/peptides as taught by Hwu et al and Waller et al.

The methods and compositions resulted from the combined teachings of Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al are indistinguishable from the methods and compositions as claimed by the present application.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Accordingly, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above modified rejection in the Amendment filed on 4/28/2010 (pages 19-23) have been fully considered but they are respectfully not found persuasive for the reasons discussed below.

1. Applicants argue basically that the primary Song reference is not enabled because the reference only provides results of gene introduction into dendritic cells using a retrovirus vector and that one skilled in the art would not reasonably conclude that any recombinant negative strand RNA virus could be used without undue experimentation because no working example using a virus vector other than a retrovirus vector is provided. Applicants refer the examiner to the teachings of Gary-Gouy (J. Interferon and Cytokine Res. 22:653-659, 2002; IDS) **which reference was not used in the above 103 rejection as evidence that the primary Song reference is not enabled**. Applicants argue that Gary-Gouy teaches that infection of CD123+CD11c- plasmacytoid dendritic cells (PDC) with Sendai virus was successful, but infection of CD11c+ myeloid dendritic cells (MDC) with Sendai virus was unsuccessful which was based primarily on the statement "The lack of production by our

sorted MDC might reflect their incapacity to internalize SV particles, which should be ingested in order to induce IFN secretion by monocytes" in the Discussion section (page 658, left column, lines 1-3). Applicants also argue that none of the cited supplemental reference makes up for the lack of a reasonable expectation of success, because none of the additional references describes a dendritic cell transduced with a negative strand RNA virus, whereas the finding of Gary-Gouy suggests that the gene transfer to dendritic cells would be unpredictable.

Firstly, the above rejection is made under 35 U.S.C. 103(a) and therefore there is no requirement that the primary Song et al reference has to teach the use of a Sendai virus vector, let alone demonstrating specifically transfection of a precursor of a dendritic cell (e.g., CD34 cells) with a Sendai virus vector. Nevertheless, Song et al taught specifically compositions and methods useful for stimulating an immune response against one or more disease associated antigens, including cancer associated antigens, by genetically modifying dendritic cells including dendritic progenitor cells, *in vivo* or *ex vivo*, wherein the dendritic cells were genetically modified by a recombinant negative strand RNA virus (e.g., vesicular stomatitis virus, paramyxoviruses, orthomyxoviruse and bunyaviruses) directing the expression of at least one disease associated antigen. At the effective filing date of the present application, the teachings of Song et al are enabled as evidenced at least by the teachings of Jin et al, Li et al, Steinman et al, Gary-Gouy et al and Lopez et al (Lopez et al, JID 187:1126-1136, April 1 2003; IDS) as discussed further below.

Secondly, the statement "The lack of production by our sorted MDC **might reflect** their incapacity to internalize SV particles, which should be ingested in order to induce IFN secretion by monocytes" in the Discussion section of the Gary-Gouy reference which was not used in the above 103 rejection **was only a speculation based primarily on the very low observed induced level of IFN-I**. It should be noted that Gary-Gouy did not use a recombinant Sendai virus vector expressing IFN-I, and demonstrated clearly that **Sendai virus can infect successfully plasmacytoid dendritic precursor cells (CD123+CD11c-), monocytes which are considered to be precursors of MDC; and even MDC cells infected with Sendai virus were shown to produce IFN-1 even though the induced level is very little** (see at least Table 1). Apart from the speculated statement there is no evidence to support that MDC cells were not infected by Sendai virus. At the effective filing date of the present application Lopez et al already demonstrated clearly that **negative-strand RNA viruses infected successfully immature dendritic cells, including the use of Sendai viruses Cantell and 52. Importantly, Lopez demonstrated that while the Sendai Cantell virus is a very potent inducer of IFN in immature dendritic cells, the Sendai 52 is a very poor inducer of this pathway** (see at least the section entitled "Type I IFN secretion by DCs infected with influenza or Sendai viruses" on page 1128 and Table 1). **Please note that about 75% and 85% of the isolated dendritic cells of Lopez do not express CD80 and CD86, respectively prior to infection with negative-strand RNA viruses (Table 4)**. Therefore, **the observed low induction of IFN-I in dendritic cells is a characteristics of the Sendai virus strain used and that the observed low**

induction of IFN-I is not an indication that dendritic cells were not successfully infected by Sendai virus (> 2 times higher expression of proteins F and HN were detected in dendritic cells infected with the poor IFN-inducing virus Sendai 52). Interestingly, **Lopez et al also demonstrated that the up-regulation of MHC and costimulatory molecules such as CD80 and CD86 in dendritic cells is independent of the induction of cytokine secretion by viruses and this upregulation was normal on DCs treated with inactivated Sendai virus** (Table 4). Moreover, Jin et al also disclosed successfully a method in which **recombinant Sendai virus was in contact and provided a highly efficient gene transfer into human cord blood CD34+ cells**, including human cord blood HSCs and more immature cord blood progenitor cells, **which are dendritic cell precursors** (see at least the abstract; page 276, col. 1, last paragraph). Furthermore, Li et al (J. Virol. 74:6564-6569, 2000; IDS) also demonstrated that **a Sendai virus vector mediated a gene transfer and expression in various types of animal and human cells, including non-dividing cells, with high efficiency**; and **Steinman et al (US 6,300,090) already successfully transfecting proliferating or non-proliferating human dendritic cells (both mature and non-mature cells) with at least a recombinant influenza viral vector which is minus-strand RNA viral vector that belongs to the same family as Sendai virus vector (see at least issued claims of US 6,300,090)**.

Accordingly, there is nothing that is unpredictable or unexpected in transfecting dendritic cells (immature and/or mature dendritic cells) and/or dendritic cell precursors (CD34+ and/or CD11c+ cells) at the effective filing date of the present application based

on the combined teachings Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al. and the state of the relevant prior art as discussed above; and an ordinary skilled artisan would have a reasonable expectation of success.

2. With respect to the primary Song reference, Applicants also argue that the reference is silent about whether CD80, CD83 or CD86 is expressed on dendritic cells.

Song et al teach clearly compositions and methods useful for stimulating an immune response against one or more disease associated antigens, including cancer associated antigens, by **genetically modifying dendritic cells including dendritic progenitor cells as well as dendritic cells having CD11c+ maker, *in vivo* or *ex vivo*, wherein the dendritic cells were genetically modified by a recombinant negative strand RNA virus.** Thus, Song et al contemplate clearly the use of CD11c+ dendritic cells and their progenitors, including immature dendritic cells. Moreover, please also note that Waller et al also taught that progenitors of dendritic cells or immature dendritic cells can be identified in many tissues, such as bone marrow and blood, based on the expression of certain cell surface markers; and that dendritic cell progenitors or immature dendritic cells are typically identified by the expression of one or more of the following markers on its cell surface **CD11c**, CD13, CD14, CD33, **CD34** or CD4.

3. With respect to Applicants' finding that the transgene expression was vey high when the Sendai virus vector was used to infect immature dendritic cells compared to mature dendritic cells, Applicants argue that neither Jin nor Li reference describes dendritic cells containing Sendai virus and once again Applicants argued that Gary-

Gouy reference (which was not used in the above 103 rejection) was unsuccessfully in infecting CD11c+ dendritic cells with Sendai virus. Applicants further cited transduction rates of <25% to 30%, 0.2% and 30% in dendritic cells reported by the Cremer, Song and Hwu references, respectively.

Firstly, please note the instant claims encompassed the use of CD34+ precursor dendritic cells being infected with Sendai virus (see at least independent claim 2 and particularly dependent claim 5). It is also noted that the terms dendritic progenitor cells, dendritic precursor cells and immature dendritic cells are used interchangeably in the prior art as evidenced at least by the cited Waller reference. Moreover, Jin et al already disclosed successfully a method in which **recombinant Sendai virus** was in contact and provided **a highly efficient gene transfer into human cord blood CD34+ cells**, including human cord blood HSCs and more immature cord blood progenitor cells; **which are known to be CD34+ dendritic progenitors or precursors**. This is also supported by the teachings of Hwu et al that showed the preparation of **recombinant dendritic cells by transforming a hematopoietic stem cell, including CD34+ cells derived from a variety of sources such as cord blood, bone marrow and mobilized peripheral blood, with a nucleic acid followed by differentiation of the stem cell into dendritic cells in the presence of GM-CSF, TNF-alpha and optionally together with IL-4.** Furthermore, Tokusumi et al taught that **the Sendai virus vector is useful for gene therapy due to its safety, high gene transfer efficiency and capacity to express a foreign gene in a high level**.

Secondly, once again Applicants misinterpreted the teachings of the Gary-Goury reference which did not show that Sendai virus did not infect CD11c+ dendritic cells. Gary-Goury showed clearly that **MDC cells infected with Sendai virus were induced to produce IFN-1 even though the induced level is very little** (see at least Table 1). Apart from the speculated statement in the Discussion there is no evidence to support that MDC cells were not infected by Sendai virus. At the effective filing date of the present application Lopez et al already demonstrated clearly that **negative-strand RNA viruses infected successfully immature dendritic cells, including the use of Sendai viruses Cantell and 52. Importantly, Lopez demonstrated that while the Sendai Cantell virus is a very potent inducer of IFN in immature dendritic cells, the Sendai 52 is a very poor inducer of this pathway** (see at least the section entitled "Type I IFN secretion by DCs infected with influenza or Sendai viruses" on page 1128 and Table 1). **Please note that about 75% and 85% of the isolated dendritic cells of Lopez do not express CD80 and CD86, respectively prior to infection with negative-strand RNA viruses (Table 4)**. Therefore, **the observed low induction of IFN-I in dendritic cells is a characteristics of the Sendai virus strain used and that the observed low induction of IFN-I is not an indication that dendritic cells were not successfully infected by Sendai virus** (> 2 times higher expression of proteins F and HN were detected in dendritic cells infected with the poor IFN-inducing virus Sendai 52).

Thirdly, it is also noted that the instant claims require infection or transduction of immature dendritic cells, CD34+ or CD11c+ precursors of dendritic cells; and not

mature dendritic cells. The primary Song reference taught explicitly **genetically modifying dendritic cells including dendritic progenitor cells as well as dendritic cells having CD11c+ maker, *in vivo* or *ex vivo*, wherein the dendritic cells were genetically modified by a recombinant negative strand RNA virus**; and Jin et al already disclosed successfully a method in which **recombinant Sendai virus** was in contact and provided **a highly efficient gene transfer into human cord blood CD34+ cells**, including human cord blood HSCs and more immature cord blood progenitor cells; **which are known to be CD34+ dendritic progenitors or precursors.**

Fourthly, the cited transduction rates of <25% to 30%, 0.2% and 30% in dendritic cells by the Cremer, Song and Hwu references, respectively, were **for experiments carried out with recombinant retroviral vectors and not by negative-strand RNA viruses, let alone by Sendai virus vector** which was known **to be useful for gene therapy due to its safety, high gene transfer efficiency and capacity to express a foreign gene in a high level** (see at least Tokusumi et al).

4. Applicants further argue that the inventors have demonstrated a surprising and unexpected beneficial effect that Sendai virus transduction into immature dendritic cells induces spontaneous maturation of transduced dendritic cells without any stimulation using LPS.

Firstly, as already noted in the above rejection the methods and compositions resulted from the combined teachings of Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al **are indistinguishable** from the methods and compositions as claimed by the present application. **Moreover, the spontaneous stimulation of**

immature dendritic cells to mature dendritic cells which are defined as dendritic cells having high expression of CD80, CD83 and CD86 is the "intrinsic property" of a Sendai virus. Therefore, this intrinsic property of a Sendai virus would occur in the methods and compositions resulted from the combined teachings of Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al; regardless whether any of these inventors are aware of. This is also an evidence that **the above 103 rejection was not** based on hindsights and/or reconstructed based on the specification of the present application.

Secondly, at the effective filing date of the present application **Lopez et al (JID 187:1126-1136, April 1 2003; IDS) already demonstrated that the up-regulation of MHC and costimulatory molecules such as CD80 and CD86 in immature dendritic cells is independent of the induction of cytokine secretion by viruses and this upregulation was normal on DCs treated even with inactivated Sendai virus** (Table 4). **Please note that about 75% and 85% of the isolated dendritic cells of Lopez do not express CD80 and CD86, respectively prior to infection with negative-strand RNA viruses (Table 4)**. Thus, at the effective filing date of the present application it was already known in the prior art as taught by Lopez et al that Sendai viruses (live or inactivated) can induce maturation of infected immature dendritic cells. Thus, there is nothing that is unexpected or surprising.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Amended claims 2, 6-7, 10-11, 13-21, 23-25 and 30-34 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-3, 7-9, 12, 15-35 of copending Application No. 11/630,532. ***This is a modified rejection necessitated by Applicant's amendment.***

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

The instant claims are directed to an isolated CD11c+ mature dendritic cell containing a Sendai virus vector; an isolated CD11c+ immature dendritic cell comprising a Sendai virus vector; a method for producing a mature dendritic cell comprising contacting a Sendai virus with a CD11c+ immature dendritic cell or with a CD34+ or CD11c+ precursor cell of a dendritic cell and differentiating the precursor cell into an

immature dendritic cell; and a method for suppressing tumor growth in a subject having a tumor using CD11c+ mature dendritic cell containing a Sendai virus vector.

Claims 2-3, 7-9, 12, 15-35 of the copending Application No. 11/630,532 are drawn to an anticancer agent comprising a dendritic cell containing a minus strand RNA virus able to replicate its genome, including a Sendai virus encoding an IFN-beta; a method for producing an anticancer agent comprising introducing a minus strand RNA virus into an immature dendritic cell or a precursor thereof and differentiating the precursor into an immature dendritic cell; and a method for suppressing a cancer comprising the step of administering an immature dendritic cell or a precursor thereof containing a minus strand RNA virus into a subject having a cancer.

The claims of the present application differ from the claims of the copending Application No. 11/630,532 in reciting specifically in all of the claims with Sendai virus vector and CD11c+ mature/CD11c+ immature dendritic cells/CD11c+ or CD34+ precursor of dendritic cell.

The claims of the present application can not be considered to be patentably distinct over claims 2-3, 7-9, 12, 15-35 of copending Application No. 11/630,532 when there are specific disclosed embodiments of the copending Application that teach that the preferred minus strand RNA viruses of the invention include paramyxoviridae virus such as Sendai virus (page 5, lines 1-36; and examples and certain dependent claims); and dendritic cells include both mature and immature CD11c+ dendritic cells as well as CD34+ precursors (page 7, line 30 continues to line 5 of page 8; line 33 of page 11 continues to line 12 of page 12; and certain dependent claims). Accordingly, the claims

of copending Application No. 11/630,532 fall within the scope of claims 2, 6-7, 10-11, 13-21, 23-25 and 30-34 of the present application.

This is because it would have been obvious to an ordinary skilled artisan to modify the claims of the copending Application by also introducing a minus-strand RNA viral vector such as Sendai viral vector into CD11c+ dendritic cells (both mature and/or immature dendritic cells) or CD11c+ or CD34+ precursors of dendritic cells for the preparation of an anticancer agent and for suppressing cancer in a subject, that support the instant claims. An ordinary skilled artisan would have been motivated to do this because these embodiments are explicitly disclosed or taught in the copending Application No. 11/630,532 as preferred embodiments.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicants' argument related to the above rejection in the Amendment filed on 4/28/2010 (page 23) has been fully considered but it is respectfully not found persuasive.

Applicants argue basically that the provisional rejection should be withdrawn since the present application is an earlier filed application with respect to the copending Application No. 11/630,532 and that if the provisional obviousness-type double patenting rejection is the last remaining rejection in the present case.

It is noted that the provisional obviousness-type double patenting rejection **is not** the last remaining rejection in the present case.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/QUANG NGUYEN/

Primary Examiner, Art Unit 1633